CARDIOVASCULAR MEDICINE

A history of arterial hypertension does not affect mortality in patients hospitalised with congestive heart failure

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Objectives: To evaluate the importance of a history of hypertension on long-term mortality in a large cohort of patients hospitalised with congestive heart failure (CHF).
Design: Retrospective analysis of 5491 consecutive patients, of whom 24% had a history of hypertension. 60% of the patients had non-systolic CHF, and 57% had ischaemic heart disease.
Setting: 38 primary, secondary and tertiary hospitals in Denmark.
Main outcome measures: Total mortality 5–8 years after inclusion in the registry.
Results: Female sex and preserved left ventricular systolic function was more common among patients with a history of hypertension. 72% of the patients died during follow up. A hypertension history did not affect mortality risk (hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.92 to 1.07). Correction for differences between the normotensive and hypertensive groups at baseline in a multivariate model did not alter this result (HR 1.08, 95% CI 1.00 to 1.17, p = 0.06). The hazard ratio was similar in patients with and without a history of ischaemic heart disease. Hence, a specific effect of hypertension in the group of patients with CHF with ischaemic heart disease, as suggested in earlier studies, could not be confirmed.
Conclusion: A history of arterial hypertension did not affect mortality in patients hospitalised with CHF.

A history of arterial hypertension is common in patients with congestive heart failure (CHF) with a prevalence ranging from 30% to more than 90% depending on the cohort and the definition of arterial hypertension.[1–3] Indeed, hypertension often has a causal role in the development of left ventricular dysfunction, either in itself or by promoting coronary artery disease.[2 4] Previous studies have shown that a history of arterial hypertension was an independent predictor of mortality in patients with reduced left ventricular ejection fraction (LVEF) in the setting of an acute myocardial infarction.[5 6] In contrast, it is unclear whether a history of hypertension affects mortality in patients with CHF,[7] and to our knowledge no previous study has been dedicated to examining this issue in detail. The results of earlier outcome studies of CHF cohorts that included arterial hypertension in multivariable survival analyses are conflicting.[1 3 8 9] Hypertension may be speculated to have a different role for outcome in CHF depending on whether the patient has ischaemic heart disease. In patients with ischaemic heart disease as the underlying cause of CHF, the presence of hypertension would theoretically simply add to the total burden of risk. Conversely, hypertension, by definition, would be positively associated with freedom from coronary artery disease in patients with pure hypertensive cardiomyopathy, decreasing the risk of myocardial ischaemia in this group. Indeed, one previous study found such an interaction between hypertension and coronary artery disease with regard to mortality risk in a selected group of patients with CHF referred for coronary angiography,[9] but the relationship remains to be confirmed in more unselected CHF populations.

The objective of the present study was to evaluate whether a history of arterial hypertension is associated with an increased mortality risk in hospitalised patients with CHF, and secondly to test the hypothesis that a possible effect of hypertension may be confined to patients with ischaemic heart disease.

METHODS

The study population for the current analysis consisted of 5548 consecutive patients hospitalised with new or worsening CHF who were screened for entry into the DIAMOND (Danish Investigations of Arrhythmia and Mortality) -CHF study. The design of the DIAMOND study has been described previously.[10] The DIAMOND-CHF study was a multicentre, randomised, controlled trial of the efficacy of the class III antiarrhythmic agent dofetilide on mortality in patients with CHF. The drug trial included 27% of the screened population with CHF and showed no significant effect of dofetilide when compared with placebo.[11] Patients were screened at departments of cardiology or internal medicine in 34 hospitals in Denmark between November 1993 and July 1996.

Criteria for entry into the DIAMOND-CHF screening registry were as follows: (1) a clinical diagnosis of heart failure made by the local investigators; and (2) at least one episode within the preceding month of shortness of breath, either on minimal exertion or at rest (New York Heart Association functional class III or IV), or paroxysmal nocturnal dyspnoea. Patients with acute myocardial infarction within the previous seven days were not included in the DIAMOND-CHF screening registry. The CHF diagnosis was a clinical one based on history and presentation. No standardised scoring system was applied. At screening, a clinical history and an ECG were obtained. In all patients an echocardiogram was recorded on videotape and evaluated in a central laboratory. Left ventricular systolic function was assessed by calculation of the wall motion index (WMI) as described previously,[12] based on a 16-segment model of the

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; DIAMOND, Danish Investigations of Arrhythmia and Mortality; HR, hazard ratio; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure; WMI, wall motion index

left ventricle with a reverse scoring system.[13] WMI multiplied by 0.3 gives an estimate of LVEF, and significant left ventricular systolic dysfunction was defined as WMI $\leqslant$ 1.2 (LVEF about $<$ 0.35). Left ventricular geometry was characterised by measurements of left ventricular end diastolic diameter obtained from two-dimensional recordings (parasternal long axis view). In 95% of the patients the quality of the echocardiogram allowed for estimation of WMI. Measures of diastolic function were not recorded. Creatinine clearance was calculated from serum creatinine values by the formula of Cockcroft and Gault.

A history of arterial hypertension was considered to be present only if the patient was taking or had previously taken drugs for high blood pressure.

Survival status was obtained by means of a computerised search by the Danish Central Personal Registry, on which all deaths in the country are registered within two weeks. The follow-up time ranged from five to eight years. Survival status was available for 5491 patients. The remaining 57 patients were lost to follow up due to emigration or due to an incorrectly recorded registration number. Only patients for whom follow up was available were included in the analyses of the present study.

The study was conducted in accordance with the Declaration of Helsinki II and approved by the Central Danish Ethics Committee.

Statistical analysis

Baseline variables were compared by continuity-adjusted χ^2 test for discrete variables and Wilcoxon rank sum tests for continuous variables. Differences in time to death between groups were analysed by a two-sided log rank test. The Kaplan–Meier method was used to construct life table plots. Hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality were obtained from Cox proportional hazard models. Initially models were constructed to include age, sex and hypertension. Subsequently models were constructed with all available covariates (except drugs). Model assumptions (proportional hazard, log linearity of continuous variables and lack of interaction) were tested and found valid. All calculations were made with SAS software V.10.5 (SAS Institute, Cary, North Carolina, USA). A value of $p < 0.05$ was considered significant.

RESULTS

Table 1 presents baseline characteristics of the patients with and without a history of hypertension. A history of hypertension was present in 24% of the patients. Male sex and previous myocardial infarction were more common among patients without a history of hypertension, but differences were small. As expected diabetes mellitus was more prevalent in the group with a history of high blood pressure. Overall, 40% of the patients had significant left ventricular systolic dysfunction (WMI $\leqslant$ 1.2), with the remaining patients having non-systolic heart failure. Heart failure with preserved systolic function was more common among patients with a history of hypertension. Angiotensin-converting enzyme (ACE) inhibitors were prescribed at discharge to more patients with hypertension. However, when the analyses were limited to those patients with a clear heart failure indication for ACE inhibitor treatment (WMI $<$ 1.2) differences were small and non-significant (78% in hypertensive patients *v* 76% in non-hypertensive patients, NS). β blockers were infrequently prescribed, but were used by more patients with hypertension than without. Among patients with left ventricular systolic dysfunction 14% of those with a history of hypertension received a β blocker compared with 8% of the normotensive patients ($p < 0.001$).

During follow up 3955 patients died (72%). A history of arterial hypertension was not associated with a higher risk of death (HR 0.99, 95% CI 0.92 to 1.07, $p = 0.8$, univariate analysis) (fig 1). Adjustment for age and sex did not significantly alter the HR for death associated with a history of hypertension (HR 1.01, 95% CI 0.94 to 1.09, $p = 0.7$). In a multivariable model containing the baseline variables from table 1 (excluding drugs), the HR for death associated with a history of hypertension was 1.08 (95% CI 1.00 to 1.17, $p = 0.06$). Hypertension history did not interact with any of the other variables included in the multivariate model. Accordingly, no significant effect of hypertension was seen in the group of patients with decreased systolic function or in the group of patients with a history of ischaemic heart disease (HR for hypertension in patients with a history of

Table 1 Clinical characteristics of patients with congestive heart failure with and without a history of arterial hypertension

	Hypertension (n = 1333)	No hypertension (n = 4158)	p Value
Age (years)	73 (54–85)	73 (52–86)	0.12
Women	44%	38%	<0.001
Duration of CHF (months)	6 (0.06–108)	8 (0.07–132)	0.009
Medical history			
Ischaemic heart disease	57%	57%	0.62
Angina pectoris	40%	40%	0.68
Myocardial infarction	34%	38%	0.03
Valvular disease	3%	4%	0.22
COPD	17%	24%	<0.001
Diabetes	20%	15%	<0.001
Current smoking	30%	25%	0.007
Atrial fibrillation	25%	24%	0.64
NYHA class III–IV	62%	63%	0.63
WMI	1.4 (0.6–2.0)	1.3 (0.5–2.0)	0.007
WMI $\leqslant$1.2	38%	42%	<0.001
LVEDD (mm)	47 (35–64)	48 (35–65)	<0.001
Creatinine clearance (ml/min)	53 (21–108)	52 (24–104)	0.40
Drugs at discharge			
ACE inhibitor	55%	50%	<0.001
β blocker	19%	11%	<0.001
Digoxin	49%	54%	0.001
Diuretic	86%	85%	0.47

Values are median (5th to 95th centiles) or percentages.
ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; LVEDD, left ventricular end diastolic dimension; NYHA, New York Heart Association; WMI, wall motion index.

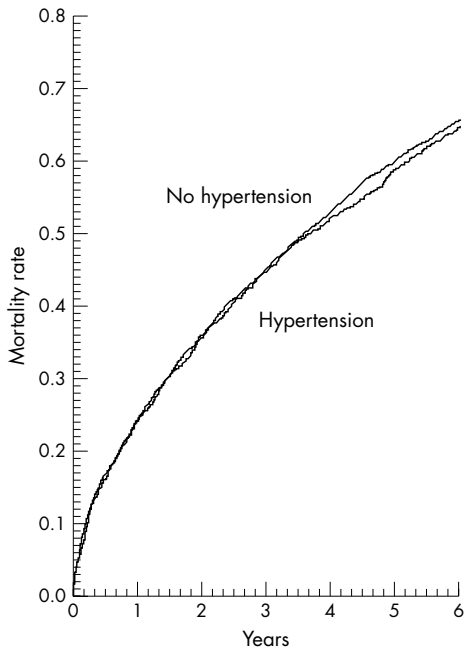

Figure 1 Kaplan–Meier plot showing mortality in 5491 hospitalised patients with congestive heart failure with and without a history of hypertension. Log rank not significant.

ischaemic heart disease 1.10, 95% CI 0.99 to 1.22, p = 0.07). Similarly, no significant interactions between hypertension and other variables were found when the analyses were restricted to only patients with a history of myocardial ischaemia.

DISCUSSION

The main result of the present study is that a history of hypertension does not increase the risk of death after hospitalisation for new or worsening CHF, irrespective of whether the patient has ischaemic heart disease. Furthermore, hypertension had no effect in patients with either depressed or preserved left ventricular systolic function.

The prevalence of arterial hypertension in the current study of hospitalised patients with CHF was lower than reported in several trials and registries, particularly from North America.[2 9 14–18] In contrast, the prevalence is comparable with findings in a number of European registries and trials.[3 19 20] Besides a possible geographical variation in the prevalence of hypertension in patients with CHF, the discrepancy between the results from various studies may relate to the definition of hypertension history. Hence, in the current study, as well as in several others with rather low hypertension prevalence, current or previous drug treatment for high blood pressure was required to indicate a history of arterial hypertension. Drug treatment of patients with and without a history of hypertension differed to some extent. As expected more hypertensive patients were discharged receiving an ACE inhibitor, but among patients with a heart failure indication for ACE inhibition, the difference between the two groups was very small. ACE inhibitors have been shown repeatedly to have on effect on outcome in heart failure or post-myocardial infarction left ventricular systolic dysfunction; this effect is at least as large, and probably even greater, in patients with a history of hypertension as the effect in patients with normal blood pressure.[21 22] The data for the current study were collected before the emergence of solid data supporting the use of β blockers in CHF, and thus the number of patients taking β blockers is small, even in the group of patients with a history of hypertension. However, despite the low number, given the considerable effect of β blockers in systolic heart failure, it must be taken into account that the proportion of hypertensive patients receiving β blockers in the present study was almost twice that of normotensive patients. Recently published data from the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) study have shown that the effect of β blockers is similar in hypertensive and normotensive patients.[23] Although differences between the groups in the current study were small, it cannot entirely be excluded that variations in drug treatment may to some extent have affected the analyses of the effect of hypertension on mortality.

The main hypothesis of the present study was that a history of arterial hypertension would be associated with decreased survival in patients with CHF. The hypothesis was primarily based on observations from previous studies in patients with left ventricular systolic dysfunction after acute myocardial infarction.[5 6 24] In addition to the epidemiological data, pathophysiological studies have shown that patients with CHF with a history of hypertension have increased sympathetic activation,[25] which is known to be associated with a poor outcome in heart failure.[26] However, in the present study a history of hypertension was not associated with an increased risk of death, irrespective of the presence of ischaemic heart disease. The finding that arterial hypertension did not increase mortality risk in CHF is in accordance with data from some previous studies,[3 15 27] whereas others found a decreased[8] or an increased[9 28] mortality in patients with a history of hypertension. The effect of hypertension on mortality reported in the latter studies, however, is present only in subgroups and is generally quite small. Thus, it appears reasonable to conclude that a history of hypertension probably does not increase mortality in unselected patients with CHF.

We further tested whether hypertension was a risk factor in patients with a history of ischaemic heart disease. The reason for performing this specific analysis was that some[5 6] although not all,[29] studies in patients with acute myocardial infarction suggested that hypertension was associated with an increased risk in the subgroup of patients with myocardial infarction with decreased LVEF. Further, some smaller studies in patients with CHF suggested that the effect of hypertension on mortality may be different in patients with and without ischaemic heart disease.[9 28] However, in the present study no significant interaction between hypertension and CHF aetiology was found, and therefore the effect of hypertension seen in the studies including patients with myocardial infarction and low LVEF cannot be extrapolated to patients with CHF and a history of ischaemic heart disease in general. It appears that the rather moderate effect of hypertension observed in patients with myocardial infarction (10–20% increased mortality) is lost when the patients with ischaemia reach the stage of symptomatic CHF. Indeed, this finding may merely be a result of ''competing risk''. In a population with heart disease but a lower risk than that of patients with CHF, the risk associated with antecedent hypertension and potential vascular complications may be apparent. In a high risk population, as studied in the present analysis, this excess risk is diluted in a very large overall risk of death.

Limitations

One limitation of the study is the accuracy of the diagnosis of arterial hypertension. The diagnosis of arterial hypertension was based on a patient's recollection or medical records. This may have led to underestimation as well as overestimation of

the diagnosis. It is assumed that patients' physicians diagnosed hypertension according to accepted Danish or European guidelines for the diagnosis of hypertension, but no testing of this assumption was possible in the design of the present study. Blood pressure recordings at the time of screening were not available in the database. However, such recordings are not likely to be very helpful in the current setting. Many hypertensive patients become normotensive when they develop CHF, and therefore relying on blood pressure recordings at the time of screening would probably lead to gross underestimation of the prevalence of antecedent hypertension. In contrast, some normotensive patients will probably present with a hypertensive blood pressure recording due to the stress associated with hospitalisation. Relying on medical history, but requiring that drug treatment for high blood pressure should have been begun at some time before the admission, therefore appeared to be a reasonable approach to test the hypothesis of the current study.

The diagnosis of CHF was based on medical history and clinical examination. For the patients with preserved LVEF, the diagnosis of CHF is likely to be less accurate. Hence, the results regarding the effect of hypertension in patients with preserved LVEF must be interpreted with some caution. Reassuringly, hypertension did not increase mortality in the large subgroup of patients with reduced LVEF, lending credibility to the overall conclusion of the study.

History of ischaemic heart disease was based on history obtained from the patient or from medical records. Given that a coronary angiogram was not available for all patients, it must be assumed that the prevalence of ischaemic heart disease is underestimated in the material.[30]

There is always a risk of selection bias in clinical studies. In the current study investigators were specifically instructed to include all patients admitted with CHF consecutively into the database (the DIAMOND registry) irrespective of whether they felt the patients would be eligible for the drug trial (the DIAMOND study). The high mean age and the overall poor prognosis seen in the registry indicate to some extent that the investigators have been careful in their screening efforts. However, it cannot be ruled out that some patients admitted with CHF were not properly screened and included in the database.

Conclusion

Although arterial hypertension is an important risk factor in the general population and probably also in patients with established coronary heart disease, it does not seem to have a major role in patients with moderate to severe CHF irrespective of the underlying cause of left ventricular failure. However, this finding should not displace emphasis from the fact that hypertension is a major risk factor for developing CHF, which may be prevented by adequate blood pressure control in the population.

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